UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen—ASD-ADHD Products Liability Litigation This Document Relates To: *All Cases*	Docket No.: 22-md-3043 (DLC)

DEFENDANTS' REPLY IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERTS' OPINIONS REGARDING ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Plaintiffs have submitted five separate briefs touting the qualifications of Drs. Andrea Baccarelli, Robert Cabrera, Eric Hollander, Stan Louie and Brandon Pearson in an attempt to distract the Court from the fact that their general causation opinions lack scientific support. But unreliable opinions do not become reliable merely because they are offered by experts with impressive degrees or jobs. And plaintiffs' request that the Court abandon its gatekeeping role and allow fringe opinions to reach jurors simply because the people offering them have long resumes would turn the well accepted principle that "law lags science" on its head. The question before this Court is: did these experts follow a reliable methodology in concluding that prenatal acetaminophen exposure can cause ADHD? The answer to that question is a resounding no.

First, plaintiffs' experts' review of the science was unreliably one-sided because: (1) the experts downplay the limitations in the few studies that reported a statistically significant association between acetaminophen use during pregnancy and a diagnosis of ADHD; (2) they rely heavily on studies using non-specific screening tools rather than ADHD diagnoses; and (3) the experts cherry-pick isolated findings from studies that tested for multiple outcomes. Plaintiffs are unable to refute any of these points.

Second, while plaintiffs' experts invoke the Bradford Hill criteria and purport to show that nearly every factor is satisfied, that does not make their methodology reliable. As explained in defendants' Reply in Support of Motion to Exclude Plaintiffs' General Causation Opinions Regarding Autism Spectrum Disorder ("ASD Reply"), filed herewith and incorporated herein, merely invoking the phrase "Bradford Hill" does not render a causation opinion reliable or admissible. Rather, experts purporting to apply the Bradford Hill criteria to establish causation must do so in a scientific manner that reliably accounts for the universe of the relevant science. *See Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at *7 (S.D.N.Y.

Sept. 3, 2021), *aff'd*, No. 22-146, 2023 WL 4837521 (2d Cir. July 28, 2023). Plaintiffs' experts have come nowhere close to meeting that standard—and instead assert that all but one of the criteria are satisfied despite clear scientific evidence to the contrary.

Third, in attempting to defend their experts' reliance on animal studies, plaintiffs fail to account for the significant physiological and psychological differences between humans and rodents that make it impossible to draw reliable conclusions about the causes of ADHD—a human condition that is characterized by uniquely human traits, such as difficulties with homework or impulsive decision-making—from observations of rodent behavior.

Finally, plaintiffs attempt to dismiss the deficiencies in Dr. Hollander's causation opinions by attributing them to mere forgetfulness. But Dr. Hollander's erroneous statements about basic epidemiological principles and his testimony denying the very same opinions on which he built his Bradford Hill analysis reveal much more than a "bad memory"; what they show is an expert who does not know the building blocks of his own opinions.

For all of these reasons, discussed further below, plaintiffs have not met their burden to establish that their experts' general causation opinions with respect to ADHD are the product of a reliable methodology.

ARGUMENT

I. PLAINTIFFS' EXPERTS MISREAD AND MISAPPLY THE RELEVANT SCIENCE.

A. Plaintiffs' Experts Rely On Studies That Did Not Properly Adjust For Genetic Confounders, While Ignoring Better-Conducted Research.

The first and most fundamental problem with plaintiffs' experts' ADHD causation opinions is that they uncritically tout the results of highly limited epidemiologic studies, while

dismissing the one study (Gustavson 2021)[1] that properly addressed genetic confounding. Plaintiffs' opposition briefs fail to show that this is a reliable methodology.

1. Plaintiffs' Experts Ignore The Significant Limitations In The Literature On Which They Rely.

Plaintiffs insist that their experts have offered reliable general causation opinions because defense experts and the FDA have conceded that multiple studies observe an association between acetaminophen exposure during pregnancy and ADHD. (*See, e.g.*, Baccarelli Opp'n at 7-9; Cabrera Opp'n at 7-9.) This argument fails for several reasons.

First, plaintiffs point to testimony from Dr. Jennifer Pinto-Martin, supposedly admitting that there were "13 statistically significant results showing a link between prenatal APAP exposure and ADHD diagnosis." (Baccarelli Opp'n at 7-8.) But Dr. Pinto-Martin merely agreed that a "forest plot" shown to her by plaintiffs' counsel accurately reflected the data, after which she explained that "each one of [the point estimates] needs to be evaluated in the context of the study from which it was derived and the data that supports that purportedly statistically significant association." (Dep. of Jennifer Pinto-Martin ("Pinto-Martin Dep.") 170:11-16 (Opp'n Ex. 25).) In addition, Dr. Pinto-Martin explained that the authors of the studies included in the forest plot "contextualize th[eir] result[s] to indicate that there are potential confounders and biases that could be driving the result" (*id.* 171:5-9), highlighting why plaintiffs' experts' claims that the studies prove a causal link are unreliable.

Plaintiffs also argue improbably that the FDA's views support their experts, contending that FDA reviews of the epidemiology "demonstrate that reasonable epidemiologists can opine"

[1] Gustavson, *Acetaminophen Use During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder – A Longitudinal Sibling Control Study*, 1(2) JCPP Advances 1 (2021) ("Gustavson 2021") (Mot. Ex. 75).

that acetaminophen exposure during pregnancy causes ADHD. (Baccarelli Opp'n at 24.) But the FDA has repeatedly taken the contrary position, most recently stating that "the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are ***unable to support a determination of causality***."[2] Plaintiffs also attempt to twist the FDA's criticisms of the existing epidemiology as praise for the quality of the studies on which plaintiffs' experts rely, asserting that "[i]n July 2022, the FDA admitted that the epidemiology was as good as it was going to get." (Baccarelli Opp'n at 24.) But the FDA merely stated that, even though a number of studies have examined the issue, "[a]s a whole, it is still unclear, despite any associations noted, whether the totality of the evidence suggests that the association between prenatal APAP and neurobehavioral and urogenital outcomes is causal."[3] It is not credible to suggest that this statement supports plaintiffs' experts' opinions.

Second, plaintiffs' suggestion that the number of studies reporting an association between prenatal acetaminophen exposure and ADHD is sufficient to support their experts' causation opinions also fails because a number of those studies simply rechurn the same data from the same cohorts—and therefore are limited by similar biases and confounding factors. Indeed, the seven studies included on the "forest plot" cited by plaintiffs used data from just four cohorts. (Mot. at 7 n.24.) Thus, while plaintiffs attempt to impress the Court with the purported volume of the literature by pointing to "17 [positive] results" (Baccarelli Opp'n at 8), those results come from only four groups of women.

Third, plaintiffs largely fail to address defendants' argument that the underlying studies have serious limitations for which the experts do not reliably account. For example, plaintiffs'

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2 *See* ECF 1105, at 1-2 (emphasis added) (citation omitted).

3 ECF 483-1 at FDACDER000114.

experts rely heavily on Baker 2020 and Ji 2020,[4] but the authors of both studies acknowledged that their results were subject to a variety of limitations, including confounding by genetic and other environmental factors. (Mot. at 20-22.) In addition, the authors of Baker 2020 acknowledged that their study did not adjust for confounding by indication. (*Id*.) As courts have noted, a study that reports an association but "reach[es] no conclusion" as to causation and notes "identifiable confounders" is "insufficient to support an expert conclusion" of causation. *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 387 F. Supp. 323, 353 (S.D.N.Y. 2019), *aff'd*, 982 F.3d 113 (2d Cir. 2020).[5]

To the extent plaintiffs address this argument in their various opposition briefs,[6] they offer a smattering of illogical arguments as to why it does not undermine their experts' causation opinions. For example, plaintiffs insist that Dr. Louie merely relied on Baker 2020 and Ji 2020 to "confirm the absence of 'confounding by indication and other known confounders,'" not unmeasured genetic confounding. (Louie Opp'n at 11-12 (citation omitted).) But Baker 2020 did not control for confounding by indication,[7] and the potential for unmeasured genetic

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[4] Baker, *Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity*, 174(11) JAMA Pediatrics 1073 (2020) ("Baker 2020") (Mot. Ex. 35); Ji, *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder & Autism Spectrum Disorder in Childhood*, 77(2) JAMA Psychiatry 180 (2020) ("Ji 2020") (Mot. Ex. 89).

[5] The authors of the other studies relied on by plaintiffs' experts that involved a diagnosis of ADHD acknowledge similar limitations. For example, the authors of Liew 2014 explicitly concede that "the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or co-exposures to other medications cannot be dismissed." (Mot. at 23 (quoting Liew, *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168(4) JAMA Pediatrics 313, 319 (2014) ("Liew 2014") (Mot. Ex. 98)).) And the authors of Liew 2019 acknowledge that they could not "rule out the possibility of other uncontrolled risk factors for ADHD that are uniquely correlated with the use of acetaminophen during the pregnancy period," such as "conditions like fever, infections, or mild pain." (*Id.* at 23-24 (quoting Liew, *Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II*, 188(4) Am. J. Epidemiol. 768, 772 (2019) ("Liew 2019") (Mot. Ex. 102)).)

[6] Plaintiffs do not address these arguments at all in their Hollander and Pearson opposition briefs.

[7] *See* Baker 2020 at 1079.

confounding renders the study's results unreliable. And while plaintiffs claim that Dr. Cabrera "acknowledged those studies' limitations" (Cabrera Opp'n at 18-19), simply mentioning limitations is not a reliable methodology; an expert must offer some analysis as to why the limitation does not affect his opinions. Dr. Cabrera fails to do so. *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 604-05 (D.N.J. 2002) (excluding expert who acknowledged that the studies on which he relied "had limitations" but failed to explain why the limitations did not affect his ultimate conclusions), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).

Plaintiffs' effort to defend Dr. Baccarelli's approach fails for similar reasons. Plaintiffs take the position that, because "[t]heoretically, a study's result could always be due to residual confounding," it was appropriate for Dr. Baccarelli to base his causation opinions on studies that expressly acknowledge that the associations observed may be due to genetic or other confounding. (Baccarelli Opp'n at 45.) Here, however, the Baker 2020 and Ji 2020 authors expressly state that the limitations on their findings, including the potential for genetic and other confounding, make it difficult to draw causal conclusions from their results.[8] *See In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 241 (S.D.N.Y. 2018) ("[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study.") (citation omitted), *aff'd*, 982 F.3d 113 (2d Cir. 2020). In addition, plaintiffs themselves concede that Leppert 2019,[9] which observed that mothers with a higher genetic risk for developing ADHD were significantly more likely to take acetaminophen during late pregnancy, provides scientific "evidence of a link between ADHD genetics and

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[8] *See id.*; *see also* Ji 2020, at 187-88.

[9] Leppert, *Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures*, 76(8) JAMA Psychiatry 834 (2019) ("Leppert 2019") (Mot. Ex. 97).

APAP use," that could be responsible for the associations observed in some of the literature.[10] (Baccarelli Opp'n at 15.) Plaintiffs assert that Dr. Baccarelli looked at this evidence and concluded "based on the data across all of the studies [that] genetic confounding was not the most likely explanation for the association[s]" observed in studies like Baker 2020 and Ji 2020. (*Id*. at 46.) But, as explained in Section I.A.2, below, this one-sided analysis is based on inherently flawed negative control studies and improperly dismisses the importance of Gustavson 2021, which found no association with proper sibling controls.[11]

Plaintiffs' oppositions fail to address numerous other study limitations that render their experts' opinions unreliable. For example:

- None of plaintiffs' oppositions explains how their experts can reasonably rely on the results of **Ji 2020** given that the study does not provide any information regarding the potential effect of acetaminophen use during pregnancy (as opposed to during or immediately prior to labor).[12] (Mot. at 22.) Moreover, the authors found that ***all*** tested cord plasma samples had detectable amounts of acetaminophen,[13] strongly suggesting some non-medicinal environmental exposure to acetaminophen or a laboratory error. (*See id.*)

- None of plaintiffs' briefs rehabilitates their experts' reliance on **Chen 2019**[14] for their causation opinions even though the vast majority of the reported associations observed were statistically insignificant (or barely significant) and the results showed the opposite of a dose response. (Mot. at 23.)

- None of plaintiffs' briefs addresses the fact that **Liew 2019** studied a cohort that was not limited to pregnant women and that the authors instead assumed that women who used acetaminophen outside pregnancy would use it equally during pregnancy. (*See*

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[10] Plaintiffs assert that "Dr. Pinto-Martin admitted that the results [of Leppert 2019] were 'barely' statistically significant and 'not incredibly powerful.'" (Baccarelli Opp'n at 15 (citation omitted).) But plaintiffs' selective quoting from Dr. Pinto-Martin's testimony fails to mention that, in the very next sentence, she reminded plaintiffs' counsel that Leppert 2019 used polygenic risk scores ("PRS"), which only capture "a fraction of the overall genetic risk. So the fact that they found anything is actually quite compelling." (Pinto-Martin Dep. 161:8-21.)

[11] *See* Gustavson 2021 at 8.

[12] *See* Ji 2020 at 187-88.

[13] *See id.* at 186.

[14] Chen, *Prenatal Exposure to Acetaminophen and the Risk of Attention- Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan*, 80(5) J. Clin. Psychiatry e1 (2019) (Mot. Ex. 58).

> Mot. at 23-24.) Further, none of plaintiffs' briefs addresses the fact that only one of the two adjusted odds ratios calculated by the Liew 2019 authors for use during pregnancy was statistically significant.[15] (*See id.* at 24.)

In short, even if plaintiffs were correct that the authorities cited by defendants merely hold that expert opinions are unreliable when they "actually ignore[]" or completely fail to mention study limitations (Baccarelli Opp'n at 44), their experts would fail that test. In reality, however, the test is more rigorous; expert opinions are inadmissible where, as here, the experts "draw[] impermissibly speculative conclusions . . . that 'exceed the limitations the authors themselves place[d] on the[se] stud[ies].'" *In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 431 (S.D.N.Y. 2016) (quoting *In re Accutane Prods. Liab.*, No. 04-2523, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009), *aff'd*, 378 F. App'x 929 (11th Cir. 2010)). For this reason, too, plaintiffs' arguments fail, and their experts' opinions should be excluded under Rule 702.

2. Plaintiffs' Experts Fail To Properly Account For Genetic Confounding.

Plaintiffs' experts' opinions that genetic confounders are not responsible for the associations on which they base their opinions are unreliable because the experts: (1) disregard Gustavson 2021, which used a sibling-control analysis, after which the association disappeared (HR 1.06, 95% CI 0.51-2.05);[16] and (2) instead premise their opinions on negative control studies that do not reliably control for genetics.

First, plaintiffs attempt to distract the Court from the importance of Gustavson 2021 by asserting that defendants' experts have admitted that the study does not "prove" that the observed

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[15] *See* Liew 2019 at 773.

[16] Gustavson 2021 at 7.

associations between acetaminophen use during pregnancy and ADHD in offspring are "all about genetics." (Baccarelli Opp'n at 47 (quoting Pinto-Martin Dep. 466:15-16).) But the question here is not whether defendants' experts have proved anything; rather, the question is whether plaintiffs' experts can reliably opine that causation has been established. *See Aycock v. R.J. Reynolds Tobacco Co.*, 769 F.3d 1063, 1069-70 (11th Cir. 2014) (district court improperly shifted the burden of proof by requiring defendants to provide alternative theory of causation; the district court "placed the burden of proof as to causation on the wrong party"). When the one properly conducted study finds no association, it raises serious doubt about a causal hypothesis, doubt that plaintiffs' experts offer no scientific basis to ignore.

Plaintiffs' silence on Gustavson is deafening. The Pearson and Hollander oppositions do not even attempt to explain these experts' failure to address the study, and while plaintiffs argue that Dr. Louie assigned "no weight" to the sibling analysis in Gustavson 2021 because it was "underpowered" (Louie Opp'n at 6), that is an *ex post facto* justification by plaintiffs' lawyers that does not appear anywhere in Dr. Louie's report. Indeed, Dr. Louie fails to mention the Gustavson 2021 sibling-control analysis results at all, despite praising the use of sibling-control studies in his report. (Dep. of Stan Louie ("Louie Dep.") 113:1-115:13 (Mot. Ex. 10).)[17] Plaintiffs cannot shore up the flaws in Dr. Louie's opinions through post hoc "elaborations by counsel." *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005); *see also Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 672-73 (6th Cir. 2010) (rejecting argument by plaintiffs' counsel in response to motion to exclude expert that "mischaracterizes [the expert's]

[17] Plaintiffs also assert that "Dr. Louie explained at his deposition" that "he assigned virtually no weight to the sibling-control results" (Louie Opp'n at 10), but Dr. Louie never so testified. Instead, Dr. Louie simply noted that he read somewhere that "the number of patients that were evaluated [in Gustavson 2021 was] relatively low" although he could not identify the actual basis of that statement. (*See* Louie Dep. 119:20-120:1.)

testimony" and opinions).

Further, plaintiffs' insistence in the Baccarelli and Louie briefs that Gustavson 2021's sibling analysis is underpowered because it involved only "34 . . . children" (Louie Opp'n at 6; *see also* Baccarelli Opp'n at 17 ("Gustavson had an operative sample size of 34.")) is based on a misrepresentation of that study.[18] For one thing, Gustavson 2021's sibling-control analysis involved 34 sibling ***groups*** in which at least one sibling had a diagnosis of ADHD, which means that the analysis involved a minimum of 68 children.[19] Thus, Gustavson 2021's sibling analysis involved ***at least as many*** children diagnosed with ADHD as Baker 2020, on which plaintiffs heavily rely.[20] Moreover, Gustavson 2021 studied 34 groups of siblings discordant on exposure and outcome where exposure was "***for 29 days or more***."[21] But the total number of groups of siblings discordant on outcome and exposure at any point during pregnancy was 306—meaning at least 612 children were included in the sibling analysis.[22] Only Dr. Cabrera noted as much in his expert report. (*See* Am. Rep. of Robert Cabrera ("Cabrera Rep.") at 140 (Mot. Ex. 6) ("306 mother[s] participated with children that were discordant on exposure as well as outcome.").)

Plaintiffs also argue that Gustavson 2021's sibling analysis is unreliable because it is

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[18] Plaintiffs' argument that Dr. Baccarelli properly dismissed Gustavson 2021 because it was based on 34 children also fails because Dr. Baccarelli has never offered that opinion. Instead, Dr. Baccarelli incorrectly asserted in this report that the Gustavson 2021 sibling analysis was underpowered because it involved "only approximately 2-3 cases of ADHD." (Mot. at 29 (citation omitted).) Plaintiffs' counsel concede Dr. Baccarelli's mistake, asserting in their briefing that Dr. Baccarelli "regrets that error" and meant to say that "34" cases of ADHD is underpowered. (Baccarelli Opp'n at 47 n.53.)

[19] *See* Gustavson 2021 at 5.

[20] *See* Baker 2020 at 1076 ("ADHD was diagnosed in 33 individuals").

[21] *See* Gustavson 2021 at 5 (emphasis added).

[22] *Id.* ("Siblings were discordant on exposure as well as outcome in 306 families."). The analysis showed that children exposed to acetaminophen for 1-7 days while in utero did not have a statistically significant increased risk of receiving an ADHD diagnosis compared to their unexposed siblings (aHR = 0.87, 95% C.I. 0.70-1.08), nor did children with 8-28 days of exposure (aHR = 1.13, 95% C.I. 0.82-1.49).

contrary to findings from Brandlistuen 2013, which plaintiffs claim demonstrated a "greater risk via a sibling-control design" by observing that "sibling[s] exposed to APAP while in utero had poorer gross motor development, communication skills, externalizing and internalizing behavior" than unexposed siblings. (Baccarelli Opp'n at 16.) But, as defendants explained in their opening brief, the Brandlistuen 2013 sibling analysis did not evaluate whether an association exists between acetaminophen use during pregnancy and ***ADHD***. (*See* Mot. at 35-36.) Instead, it found that, at three years of age, siblings exposed to acetaminophen were more likely to experience adverse outcomes, as measured by a broad developmental screening tool, than unexposed siblings. (*Id.*) As set forth in Section I.B, below, the results of studies that employ screening tools as endpoints do not provide a reliable basis for an ADHD causation opinion.

Second, plaintiffs' experts improperly rely on certain "negative control" studies as evidence that genetic confounding does not play a role in the associations observed between prenatal acetaminophen exposure and the development of ADHD. (*See* Mot. at 30-31.) Plaintiffs argue that the "negative control" studies relied on by their experts, which examined "whether a woman's use of APAP before or after pregnancy was associated with" neurodevelopmental disorders, ruled out genetics as the cause of the observed associations between acetaminophen use during pregnancy and ADHD. (Baccarelli Opp'n at 12-14.) According to plaintiffs, "if women who genetically are more likely to have children with ASD and ADHD are somehow more likely to consume APAP . . . then they should be more likely to take more APAP before and after pregnancy as well." (*Id.*) But this assertion—like plaintiffs' experts' opinions—is contrary to the science demonstrating that women who take acetaminophen during pregnancy are significantly more likely to have chronic medical conditions, mental

diseases and psychiatric conditions, all potential confounders for the observed associations.[23]

Plaintiffs and their experts also greatly overstate the import of the negative control studies they cite. For example, plaintiffs argue that "the Stergiakouli study . . . showed no association between a mother's use of APAP after pregnancy and her child's risk of hyperactivity, emotional, and conduct problems" and instead suggested that the "associations 'are consistent with an intrauterine mechanism,' *i.e.*, a causal link." (Baccarelli Opp'n at 13 (citation omitted).) But the authors themselves disclaimed any suggestion that their findings were "clinically significant or suggest that there should be a change in public health advice," noting that "this is explicitly stated in the abstract and discussion."[24] Plaintiffs also assert that their experts properly cite Ystrom 2017's negative control analysis, which purportedly showed "no association between a mother's use of APAP before pregnancy and her child's risk of ADHD." (Baccarelli Opp'n at 13-14.) But Ystrom 2017 also conducted a negative control analysis focusing on ***paternal use*** of acetaminophen before pregnancy and found that it was "as strongly associated with ADHD . . . as the corresponding maternal prenatal use," leading the Ystrom 2017 authors to conclude that their study results did not "provide definitive evidence for or against a causal relation[ship]."[25] (*See* Mot. at 27.)

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[23] *See* Taagaard, *Paracetamol Use Prior to & in Early Pregnancy: Prevalence & Patterns Among Women With & Without Chronic Medical Diseases*, 89(8) Br. J. Clin. Pharmacol. 2582 (2023) (Mot. Ex. 141) (women with chronic medical disorders are more likely to use acetaminophen during pregnancy, including women with mental diseases (mental diseases aOR = 2.74, CI 95% 1.67-4.49)); Stergiakouli, *Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding*, 170(10) JAMA Pediatrics 964, 966 (2016) ("Stergiakouli 2016") (Mot. Ex. 138) (finding higher rates of psychiatric illness among women who took acetaminophen during pregnancy versus women who took it postnatally (10.2% v. 8.1%, respectively)).

[24] Stergiakouli, *Acetaminophen in Pregnancy and Adverse Childhood Neurodevelopment—Reply*, 171(4) JAMA Pediatrics 396, 397 (2017). Copies of all studies cited herein and not previously provided are attached to the Declaration of Kristen L. Richer as Exs. 2-14.

[25] Ystrom, *Prenatal Exposure to Acetaminophen and Risk of ADHD*, 140(5) Pediatrics 1, 4, 7 (2017) ("Ystrom 2017") (Mot. Ex. 165). Plaintiffs' briefing also fails to address Ystrom 2017's finding that maternal use of acetaminophen for less than eight days was negatively associated with ADHD, which—according to the authors—indicated that acetaminophen exposure "could be ***beneficial*** with regard to fetal development" in certain

In short, both plaintiffs and their experts attempt to stretch the limited science addressing the potential association between prenatal acetaminophen exposure and the development of ADHD beyond the study authors' conclusions, all while downplaying the importance of contrary studies that undermine their causal theories. This is not a reliable scientific methodology. *See In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075, 1194, 1198-1204 (S.D. Fla. 2022) (excluding plaintiffs' causation experts, in part, due to their failure to address confounding variables).

B. Studies That Do Not Involve A Clinical Diagnosis Of ADHD Cannot Reliably Support Plaintiffs' Experts' Causation Opinions.

As defendants explained in their opening brief, studies that purport to evaluate whether prenatal acetaminophen exposure is associated with potential symptoms of ADHD cannot provide a basis for expert causation opinions because mere symptoms are not reliable proxies for an actual clinical diagnosis. (*See* Mot. at 31-37; *see also* ASD Br. at 38-40 (ECF 1160).) Plaintiffs concede that these so-called "proxy" studies are less "probative" than studies involving a diagnosis as an endpoint, but insist that this goes only to the weight of their experts' testimony, not its admissibility. (*See, e.g.*, Hollander Opp'n at 16.) As explained in defendants' ASD Reply, this argument is inconsistent with the relevant law, which makes clear that studies that use screening tests rather than diagnoses as an endpoint do not provide "reliable support for the theory that" in utero exposure to acetaminophen causes neurobehavioral conditions such as ADHD and ASD.[26] (ASD Reply at 23.) The reason is simple: screening tests are designed to be over-inclusive to ensure that they capture anyone who ***might*** have ADHD; as a result, they

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circumstances. (Mot. at 27 & n.68 (quoting Ystrom 2017 at 6-7).)

[26] This position is also fundamentally inconsistent with Dr. Baccarelli's claim that he disregarded Trønnes 2020 because it "did not have ADHD as an endpoint." (Am. Rep. of Andrea Baccarelli at 116 (Mot. Ex. 2).)

sweep in people with other conditions, or not condition at all.

In addition, plaintiffs' assertion that the FDA and JJCI have admitted that studies using screening tools as an endpoint are helpful for assessing general causation (*see, e.g.*, Baccarelli Opp'n at 41; Hollander Opp'n at 13), is false (*see* ASD Reply at 20-23). The FDA has specifically stated that studies attempting to measure proposed associations between environmental exposures and the development of neurobehavioral conditions should use "a clinical diagnosis" as the outcome. (ASD Reply at 22.) And while JJCI looked at all the literature as part of its pharmacovigilance, it never suggested that these studies are indicative of causation. (*Id.*)

Plaintiffs also insist that "multiple peer-reviewed publications" have acknowledged that the screening instruments used in the studies on which their experts rely are "well validated methods" that serve as reliable "proxies for . . . [an] ADHD diagnos[is]." (Hollander Opp'n at 10-11.) Not so. For example:

- ***Strengths & Difficulties Questionnaire ("SDQ").*** Plaintiffs assert that Russell 2013 and Overgaard 2019 "validate" the use of this screening method for ADHD. (Hollander Opp'n at 11.) But the authors of Russell 2013 stated that they "do not currently recommend using the SDQ as a screening tool for . . . clinical practice due to the high number of false positives and limitations of case definition in our study."[27] Overgaard 2019 similarly recognizes the difficulty of setting a threshold for interpreting SDQ results that would yield meaningful diagnostic results, noting that a threshold capable of providing the requisite sensitivity and specificity would "increase[] the number of false positive diagnoses, resulting in a very low probability of correctly identifying a child with ADHD."[28] And the FDA has stated that "use of the SDQ, a screening tool, to 'diagnose' the study outcome is problematic"[29] and, additionally, that "some of the scales on the SDQ

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[27] Russell, *The Strengths and Difficulties Questionnaire as a Predictor of Parent-Reported Diagnosis of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder*, 8(12) PloS One 1, 7 (2013) (Mot. Ex. 124).

[28] Overgaard, *The Predictive Validity of the Strengths and Difficulties Questionnaire for Child Attention-Deficit/Hyperactivity Disorder*, 28 Euro. Child Adolesc. Psychiatry 625, 631 (2019).

[29] ECF 483-1 at FDACDER000041; *see also* ECF 483-1 at FDACDER000017 (noting that the SDQ's "minimiz[ation of] false negatives at the expense of false positives is an appropriate balance for a screening

do not appear to be directly relevant to ADHD."[30]

- ***Child Behavior Checklist ("CBCL").*** Brandlistuen 2013, on which plaintiffs' own experts rely, expressly notes that the CBCL is not a "diagnostic tool" and therefore, the authors could not "determine the clinical importance of" their CBCL findings.[31] In addition, most of the publications plaintiffs cite as validating the CBCL as a diagnostic proxy address ASD, not ADHD. While plaintiffs cite Spencer 2018 as purportedly validating the use of the CBCL, that study recognizes that the CBCL is only a screening method and expressly notes that applying a CBCL threshold that is sufficiently sensitive to "detect[] . . . high-risk children . . . would come at the expense of a higher false-positive rate."[32] Plaintiffs also cite Biederman 2021[33] as "validating" the use of the CBCL to detect ADHD (Hollander Opp'n at 11), but that study actually examined the CBCL's ability to predict ***other*** conditions and did not report on the validity of the CBCL as a diagnostic tool for ADHD.[34]

- ***Ages & Stages Questionnaire ("ASQ").*** While plaintiffs assert that the ASQ is "an effective diagnostic tool of developmental delay and/or disturbances" (Hollander Opp'n at 11-12), they do not identify any published literature validating the tool for any diagnostic disorder, much less literature identifying the ASQ as a valid diagnostic tool for ADHD specifically.[35]

- ***Developmental & Well-Being Assessment ("DAWBA").*** Plaintiffs argue that the DAWBA is a valid diagnostic tool for ASD and ADHD (*see* Hollander Opp'n at 12), but the only study they cite that addresses the DAWBA is Ruisch 2018. That study examined associations between paracetamol use and oppositional defiance disorder and conduct disorder—not ADHD.[36] Indeed, Ruisch 2018 expressly

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instrument," but "might present a limitation for research purposes").

30 ECF 483-1 at FDACDER000008.

31 Brandlistuen, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study*, 42(6) Int'l J. Epidemiol. 1702, 1711 (2013) ("Brandlistuen 2013") (Mot. Ex. 50).

32 Spencer, *Screening for Attention-Deficit/Hyperactivity Disorder and Comorbidities in a Diverse, Urban Primary Care Setting*, 57(12) Clin. Pediatrics 1442, at 7 (2018).

33 Biederman, *The Child Behavior Checklist Can Aid in Characterizing Suspected Comorbid Psychopathology in Clinically Referred Youth with ADHD*, 138 J. Psychiatr. Res. 477 (2021) (Opp'n Ex. 90).

34 *See id.* at 3.

35 The authors of Brandlistuen 2013, which utilized the ASQ, concluded that "because clinical assessments with diagnostic tools were not available in this study, we could not determine the clinical importance of the difference observed." Brandlistuen 2013 at 1711.

36 *See* Ruisch, *Pregnancy Risk Factors in Relation to Oppositional-Defiant and Conduct Disorder Symptoms in the Avon Longitudinal Study of Parents and Children*, 101 J. Psychiatr. Res. 63 (2018).

excluded individuals with ADHD symptoms from its analysis.[37]

In short, plaintiffs' experts' methodologies are also unreliable because they purport to base their causation opinions on non-diagnostic studies that cannot assess whether an association exists between prenatal acetaminophen exposure and a diagnosis of ADHD. This, too, requires exclusion of their opinions.

C. Plaintiffs' Experts Improperly Rely On Cherry-Picked Outcomes From Studies With Multiple, Inconsistent Findings.

Plaintiffs' argument that their experts did not engage in cherry-picking (Baccarelli Opp'n at 47; Cabrera Opp'n at 19; Louie Opp'n at 9; Hollander Opp'n at 20-21) is refuted by their own touted "forest plot," which omits numerous findings that do not support their positions. For example:

- ***Gustavson 2021.*** Plaintiffs' forest plot includes a positive (but statistically insignificant) sibling-control result for individuals with more than 28 days of exposure, but omits the null sibling-control result for individuals with 1-7 days of exposure (HR 0.75, 95% CI 0.56-1.03) and the null sibling-adjusted result for individuals with 8-28 days of exposure (HR 0.93, 95% CI 0.59-1.46).[38]

- ***Ystrom 2017.*** Plaintiffs' forest plot includes results for individuals with more than 29 days of exposure, but omits the negative association observed for individuals with 1-7 days of exposure (aHR = 0.90, 95% CI 0.81-1.00) and the statistically insignificant results for individuals with 8-14, 15-21 and 22-28 days of exposure.[39] Additionally, the forest plot does not include data points from Ystrom 2017 showing that when the authors controlled for fever & infection, pain conditions, and non-specified indications, 11 of the 14 reported results were not statistically significant.[40]

- ***Liew 2014.*** The forest plot includes three statistically significant results from this study but omits 19 other non-significant results, including results broken down by

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37 *See id.*

38 Gustavson 2021 at 7.

39 Ystrom 2017 at 6.

40 *See id.*

trimester and duration of use that show no dose response.[41]

Plaintiffs also fail to respond substantively to defendants' argument that plaintiffs' experts' reliance on selected findings in studies that consider numerous potential endpoints is methodologically improper due to the risk of "multiplicity bias." (Mot. at 39-40.) Plaintiffs complain that this criticism was "made for litigation" and that defendants have failed to present evidence that "all of the results in this literature could be the result of chance." (Baccarelli Opp'n at 49.) But that mischaracterizes the import of defendants' argument. It is well recognized that studies involving multiple endpoints suffer from "multiplicity" problems because there is a higher likelihood that any one statistically significant positive association is the result of chance. (*See* Bio. Plaus. Br. at 35-36 (ECF 1165).)[42] Because plaintiffs' experts pluck isolated positive findings from studies, there is a distinct possibility that some of those positive results are the result of chance. (*See* Mot. at 2, 39-40.) This critique is not "made for litigation"; to the contrary, epidemiologists typically employ a correction known as the Bonferroni (or multiplicity) adjustment to account for multiplicity problems. And the FDA has raised this concern as well, noting that studies indicating an association between acetaminophen use during pregnancy and conditions such as ADHD have failed to properly adjust for the possibility of multiplicity error, limiting their value in assessing a causal link.[43]

For these reasons, too, plaintiffs' experts' general causation opinions are unreliable.

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41 *See* Liew 2014 at 317-18.

42 Leppert 2019 properly corrected for multiple testing to avoid chance findings resulting from testing numerous different endpoints. *See* Leppert 2019 at 836.

43 ECF 483-1 at FDACDER000041 (addressing Stergiakouli 2016 and noting that "[t]he multiple hypotheses testing without adjustment for multiplicity introduces the risk of false positive association between APAP and the measured outcomes"); ECF 483-1 at FDACDER000109 (noting that "in studies attempting to evaluate causal associations, not accounting for multiple comparisons increases the risk of a type I error (incorrectly rejecting the null) due to chance alone").

II. PLAINTIFFS' EXPERTS' BRADFORD HILL ANALYSES WERE UNRELIABLE.

Throughout their briefs, plaintiffs suggest that merely invoking the Bradford Hill criteria inoculates an expert from a Rule 702 challenge, regardless of how the criteria are applied. (*See, e.g.*, Baccarelli Opp'n at 1, Cabrera Opp'n at 26-27; Hollander Opp'n at 2.) That is obviously not the case; rather, as explained in defendants' ASD Reply, plaintiffs bear the burden of demonstrating that their experts applied the factors reliably, "thoroughly analyze[d] the strengths and weaknesses of any inconsistent research and sufficiently reconcile[d] [their] opinion[s] with contrary authority." (ASD Reply at 11 (quoting *Daniels-Feasel*, 2021 WL 4037820, at *15).) Drs. Baccarelli, Cabrera and Hollander did none of these things; if they had, they would not have been able to reach causation opinions for this litigation.

A. Plaintiffs' Experts' Analyses Of Strength Of Association Ignore The Meaning Of The Word "Strong."

Plaintiffs assert that all of their experts reliably analyzed the strength of association consideration, but despite filing separate briefs for each expert, they simply rely on their Baccarelli arguments for the other experts as well. (Baccarelli Opp'n at 50-52; Cabrera Opp'n at 28 (incorporating Baccarelli Opp'n at 48-58); Hollander Opp'n at 21 (same).) According to plaintiffs, Dr. Baccarelli's strength analysis was reliable because he "candidly admitted that 'in many of the studies, the magnitude of the association was moderate, with risk ratios between 1.0 and 2.0.'" (Baccarelli Opp'n at 50 (citation omitted).) But admitting that the associations were not strong does not somehow justify concluding that the strength consideration is satisfied. To the contrary, this is a tacit admission that Dr. Baccarelli's strength opinion is not defensible. As Dr. Cabrera expressly admits, "an odds ratio between 1 and 2 is deemed low" (Cabrera Rep. at 134, 189), and plaintiffs' refrain that a causal link has been established between second-hand smoke and lung cancer even though studies observed risk ratios less than 2.0 (Baccarelli Opp'n

at 51) misses the point. In the case of second-hand smoking, the other considerations were so compelling that a causal relationship was established ***despite*** a weak association. That does not make it appropriate to pretend that weak study results were in fact strong. (*See* Mot. at 42.)

Plaintiffs also argue that the "Ji and Baker studies showed risk ratios of above 2.0 and indeed 3.0" (Baccarelli Opp'n at 50), but the Bradford Hill factors assess the totality of the literature, not isolated study results. *In re Zantac*, 644 F. Supp. 3d at 1230 (excluding general causation opinion where one study showed a statistically significant increase over 2.0 but other studies reported lower point estimates, both significant and insignificant). And plaintiffs' experts' outsized emphasis on the findings in these two studies is particularly problematic because low associations are more likely to be the result of bias or confounding, and neither Baker 2020 nor Ji 2020 "adjust[ed] for genetic confounders." (Mot. at 20-22.)

B. <u>The Relevant Epidemiological Evidence Is Inconsistent.</u>

Plaintiffs' briefing fails to address Dr. Cabrera's admission that the "association between prenatal APAP exposure and adverse neurodevelopmental outcomes in children . . . is not consistent across all studies, and some studies did not find significant associations or found mixed results." (Mot. at 44-45 (quoting Cabrera Rep. at 160).) Instead, they assert that the "consistency factor" is "obviously" satisfied because "[n]umerous study authors have said explicitly that the results are consistent." (Baccarelli Opp'n at 52.) But the literature they cite for this proposition predates Gustavson 2021's finding that there is no statistically significant association between acetaminophen use during pregnancy and ADHD after properly controlling for genetics. Publications that do not account for the current state of the science cannot support a finding that a consistent association has been demonstrated. *See, e.g.*, *Daniels-Feasel*, 2021 WL 4037820, at *9 (consistency factor not met where analysis "fail[ed] to note" studies with contrary

findings).[44] In addition, as explained in defendants' ASD Reply, plaintiffs' experts' consistency opinions are premised on a disregard of statistical significance (*see* Baccarelli Opp'n at 53), contrary to basic epidemiological principles and relevant law (*see* ASD Reply at 30-31).[45]

C. Drs. Baccarelli, Cabrera And Hollander Lack A Scientific Basis To Downplay The Specificity Criterion.

Plaintiffs' assertion that their experts reliably evaluated the specificity factor because they concluded that this factor "is ***not*** satisfied—the answer [defendants] agree with" (Baccarelli Opp'n at 53) is not a valid response to defendants' arguments (*see* ASD Reply at 31). The problem is that plaintiffs downplay the relevance of this consideration. Plaintiffs have no substantive answer to that criticism. (*See* Baccarelli Opp'n at 53; ASD Reply at 31.)

D. Drs. Baccarelli, Cabrera And Hollander Lack Reliable Evidence Of A Dose Response.

Plaintiffs do not meaningfully respond to any of defendants' critiques of their experts' dose-response opinions, including the fact that some of the studies admittedly did not measure the dose of acetaminophen taken by the mother and others show declining or inconsistent associations with increased maternal exposure to acetaminophen. (*See* Mot. at 46-49.)[46]

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[44] Plaintiffs' assertion that the FDA's 2022 review of the epidemiological evidence found a "consistent association" between prenatal acetaminophen use and ADHD (Baccarelli Opp'n at 53 (quoting ECF 483-1 at FDACDER000114)) misrepresents the FDA's findings. Based on its review of the Alemany 2021 meta-analysis—on which plaintiffs heavily rely in defending their experts' consistency assessments—the FDA noted that the observed associations "are inconsistent by trimester of exposure." ECF 483-1 at FDACDER000115. In addition, the FDA concluded that "there are still study limitations and ***inconsistent*** study findings that prohibit causal interpretations of the association between APAP exposure and functional neurobehavioral outcomes as well as urogenital outcomes." ECF 483-1 at FDACDER000115 (emphasis added).

[45] Plaintiffs fail to address, much less refute, the fact that even the studies that report a statistically significant association are inconsistent with one another in terms of which trimesters of exposure show an association. (Mot. at 44-45.)

[46] Plaintiffs also fail to grapple with findings that women who take acetaminophen for 20-30 days, i.e., women with "long term" use, are meaningfully different from short-term users in that they have higher "self-reported depression or anxiety" and higher "antidepressant use." Bandoli, *Acetaminophen Use in Pregnancy: Examining Prevalence, Timing & Indication of Use in a Prospective Birth Cohort*, 34(3) Paediatr. Perinat. Epidemiol. 237, 243 (2020).

Plaintiffs' experts cannot reliably opine that a dose-response relationship has been established when the actual results of the relevant universe of studies do not support that conclusion. *See Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 188 (E.D.N.Y. 2001) (excluding expert who relied on studies where "[f]ew, if any, dose-response relationships were reported"), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

E. Drs. Baccarelli, Cabrera And Hollander Do Not Offer Reliable Opinions About Biological Plausibility.

Plaintiffs' claim that their experts adequately assessed whether there is a biologically plausible mechanism by which in utero acetaminophen exposure causes ADHD (*see* Baccarelli Opp'n at 55; Cabrera Opp'n at 29-31; Hollander Opp'n at 21-22) fails for all the reasons set forth in defendants' Biological Plausibility Reply, filed herewith and incorporated herein. In a nutshell, plaintiffs' experts have offered, at best, various mechanistic hypotheses; they have not identified reliable evidence that any one of them is a scientifically plausible causal mechanism specific to ADHD.

F. Drs. Baccarelli, Cabrera And Hollander's Opinions That The Epidemiologic Evidence Is Coherent Are Not Reliable.

Plaintiffs either ignore or fail to refute defendants' arguments regarding the coherence consideration.

Dr. Cabrera asserts that coherence is satisfied because acetaminophen "is a known 'stressor' that generates oxidative stress," to which the "fetal brain is most susceptible." (Cabrera Opp'n at 31.) As explained in defendants' Biological Plausibility Memorandum and Reply, however, the relevant science does not support a finding that acetaminophen leads to oxidative stress in the fetal brain, let alone that any such stress causes ADHD. (*See* Bio. Plaus. Br. at 21-28; Bio. Plaus. Reply at 12-14.)

Dr. Baccarelli and plaintiffs' other experts take a different approach to coherence,

opining that their theories are "consistent with studies showing a link between a country's ***ASD*** rates and its use of APAP, and data suggesting that the rates of ASD and APAP use appear to have moved in tandem." (Baccarelli Opp'n at 55 (emphasis added).) But even if that were true for ASD, it is not true for ADHD. The prevalence of acetaminophen use during pregnancy varies dramatically by geography, with some countries reporting usage rates 20 or more percentage points higher than other countries, but no corresponding differences in the rates of ADHD. (*See* Mot. at 51-52.)

G. Plaintiffs' Experts' Opinions On Temporality Are Speculative.

As explained in defendants' ASD Reply, plaintiffs' experts lack a reliable basis to conclude that prenatal exposure to acetaminophen in the studies on which they rely preceded the biological changes that lead to ADHD. (*See* ASD Reply at 34.) The reason for this failure is self-evident. Because science has not yet determined when those changes occur, it is impossible to know whether a mother's use of acetaminophen occurred before that critical period or after.

H. Plaintiffs' Experts' Opinions On Analogy And Experiment Are Illogical And Unsupported.

Plaintiffs essentially concede that their experts' approaches to analogy do not differentiate between ASD or ADHD, and that they turn on comparisons to valproic acid. As explained in defendants' ASD Reply and opposition to plaintiffs' motion to exclude the opinions of Dr. Pinto-Martin, comparisons to valproic acid are inapposite for a host of reasons, including that the study results were stronger and exposure data are more accurate. (*See* ASD Reply at 34; *see also* Pinto-Martin Opp'n at 34-35 (ECF 1241).) Plaintiffs take a similar approach with respect to the experiment factor, perfunctorily asserting that the experts' causation opinions are supported by "experimental data" in the form of unspecified "animal studies, lab studies, ecological studies, and human pharmacokinetic studies." (Baccarelli Opp'n at 57.) This

argument fails for all the reasons set forth in Section III below and in defendants' Biological Plausibility Brief, and Biological Plausibility Reply Brief, incorporated herein.

* * *

In short, plaintiffs' arguments only serve to underscore the unreliability of their experts' Bradford Hill analyses.

III. PLAINTIFFS' EXPERTS CANNOT FILL THE ANALYTICAL GAPS IN THEIR OPINIONS WITH ANIMAL STUDIES.

Plaintiffs argue that studies of rodents exposed to acetaminophen are equally applicable to humans because "[b]oth species 'undergo rapid brain development *in utero* and after birth" and share some "underlying brain architecture" (Cabrera Opp'n at 5-6 (citation omitted)), but that is far too low a bar to render animal studies relevant to causation. There are obvious, significant differences between human and rodent brains and behaviors—especially with respect to the areas of the brain that control the behaviors relevant to an ADHD diagnosis, behaviors that are not exhibited by rodents and cannot be assessed in animals: e.g., making "careless mistakes in schoolwork." (Mot. at 54 (citation omitted).)[47]

Plaintiffs' experts' reliance on rodent studies is problematic for other reasons as well, all of which go unanswered in plaintiffs' opposition briefs. For example, several of the studies on which they rely addressed behaviors that have no possible relevance to ADHD, whether exhibited in rats or humans, such as sexual behaviors. (*See* Mot. at 55.) Nor do plaintiffs offer any justification for their experts' reliance on studies dosing ***adult*** mice with acetaminophen (e.g., Ishida 2017), exposures that have no bearing on in utero development. (*See id*.)

[47] Indeed, Dr. Pearson stated in Baker 2023 that it is "possible that ADHD is too complex a human disorder to be translated into animal behavior." Baker, *Sex-Specific Neurobehavioral and Prefrontal Cortex Gene Expression Alterations Following Developmental Acetaminophen Exposure in Mice*, 177 Neurobiol. Dis. 1, 11 (2023) ("Baker 2023") (Mot. Ex. 36).

Plaintiffs do briefly attempt to defend their experts' cherry-picking of favorable results within the relevant animal literature, but this effort fails as well. According to plaintiffs, Dr. Cabrera did not cherry-pick positive findings because he noted that the studies he relied on also had negative findings. (*See, e.g.*, Cabrera Opp'n at 25 (asserting that "Dr. Cabrera accurately reports the Klein (2020) study's conclusion that APAP is a developmental neurotoxicant while, as [d]efendants acknowledge, also reporting certain findings within that study that did not support that conclusion.").) But plaintiffs—like Dr. Cabrera—are unable to explain ***why*** he relied on the positive findings of the studies he cited while dismissing the negative findings that undermine his causation opinions. This renders his opinions unreliable and inadmissible. *See Magistrini*, 180 F. Supp. 2d at 604-05 (while expert acknowledged that some studies on which he relied "had limitations," he failed to grapple with those studies or pay them proper attention in reconciling them with his ultimate conclusions).

Plaintiffs ignore numerous other examples of cherry-picking altogether. For example, plaintiffs do not address Dr. Cabrera's reliance on allegedly supportive findings from Saeedan 2018[48] and Baker 2023 in reaching his opinions, while ignoring other, directly contrary observations in those same studies, including decreased "hyperactivity" in Baker 2023 and decreased "locomotor activity" in Saeedan 2018. (*See* Mot. at 55-56.) Plaintiffs also fail to dispute that the lead author of Baker 2023, a study of rodent behavior on which Dr. Cabrera relies as "clear evidence of causation" (Cabrera Rep. at 126-27) expressly acknowledged that it would be inaccurate to state that any of the exposed rodents exhibited "ADHD-like" behaviors (*see* Mot. at 56 (ECF 1162)).

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[48] Saeedan, *Effect of Early Natal Supplementation of Paracetamol on Attenuation of Exotoxin/Endotoxin Induced Pyrexia & Precipitation of Autistic Like Features in Albino Rats*, 26 Inflammopharmacology 951 (2018) ("Saeedan 2018") (Mot. Ex. 125).

For all of these reasons, the animal studies cited by plaintiffs' experts cannot reliably support their causation opinions.

IV. DR. HOLLANDER'S OPINIONS SHOULD ALSO BE EXCLUDED BECAUSE HE LACKS THE REQUISITE FAMILIARITY WITH BOTH THE RELEVANT SCIENCE AND HIS OWN OPINIONS.

Finally, plaintiffs are unable to save Dr. Hollander from his own confession that he does not understand many of the opinions included in his report. (Mot. at 57-58.) Plaintiffs broadly assert that defendants' only criticism of Dr. Hollander is that he failed to "memorize all aspects of the sprawling literature in this case" or every word of his report. (Hollander Opp'n at 23.) But the problems revealed during Dr. Hollander's deposition testimony—which plaintiffs fail to specifically address—go far beyond mere "memory lapses." (*Id*. at 22-23 (citation omitted).)

Among other things, Dr. Hollander contradicted basic findings from Masarwa 2018, a study on which he purports to base his opinions. (*See* Mot. at 57-58.) In addition, Dr. Hollander misstated basic principles of epidemiology, including the meaning of the term statistical significance. (*Id*.) He also expressly disagreed with statements that were quoted verbatim to him from his own report. (*Id*.) None of this relates to Dr. Hollander's memory; rather, it reflects his total lack of familiarity with the substance of his own report. Plaintiffs make no attempt to distinguish the multiple cases cited by defendants in which experts were excluded in similar circumstances. (*See* Mot. at 57-58 (citing *Caruso v. Bon Secours Charity Health Sys. Inc.*, No. 14-4447, 2016 WL 8711396, at *6 (S.D.N.Y. Aug. 5, 2016) (excluding expert whose deposition testimony "revealed critical gaps in h[is] knowledge" of the studies on which he purportedly relied and the opinions in his report), *aff'd*, 703 F. App'x 31 (2d Cir. 2017); *Richman v. Respironics, Inc.*, No. 08-9407, 2012 WL 13102265, at *13 (S.D.N.Y. Mar. 13, 2012) (excluding expert whose opinions "contradict[ed] his own deposition testimony")).)

CONCLUSION

For the reasons set forth above, and those set forth in defendants' opening brief, the Court should exclude the opinions offered by Drs. Baccarelli, Cabrera, Hollander, Louie and Pearson that in utero exposure to acetaminophen is capable of causing, or increases the risk of, ADHD.

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Respectfully submitted,

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